

CUTTING, Simon M.
Appl. No. 10/506,749
January 22, 2008

AMENDMENTS TO THE SPECIFICATION:

In the specification, in relation to the paragraph numbers of the published application, US 2005/0287168 A1:

Delete paragraph number [0002] in its entirety and replace it with the following new paragraph number [0002]:

[0002] This invention relates to the germination of spores and in particular, but not exclusively, to spores of *Bacillus* species of bacteria and uses thereof.

Delete paragraph number [0010] in its entirety and replace it with the following new paragraph number [0010]:

[0010] It is an aim of the present invention to provide a spore in which said spore may be genetically modified to produce a medicament upon germination into a vegetative cell.

Delete paragraph number [0011] in its entirety and replace it with the following new paragraph number [0011]:

[0011] Accordingly, the present invention, provides a spore which is genetically modified with genetic code comprising at least one genetic construct encoding a therapeutically active compound and a targeting sequence or a vegetative cell protein.

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Delete paragraph number [0013] in its entirety and replace it with the following new paragraph number [0013]:

[0013] It is a further advantage of the invention that the spores elicit an immune response at the mucosal membranes. This makes the vaccination more effective against mucosal pathogens e.g. *S. typhi*, *V. cholera* and *M. tuberculosis*.

Delete paragraph number [0015] in its entirety and replace it with the following new paragraph number [0015]:

[0015] It is a further advantage of the present invention in that when said spore is administered to an animal, said spore germinates into a vegetative cell, said vegetative cell expresses said chimeric gene, wherein said chimeric gene comprises said medicament and said protein in order to elicit an immune response against said antigen.

Delete paragraph number [0017] in its entirety and replace it with the following new paragraph number [0017]:

[0017] Preferably the therapeutically active compound is an antigen or a medicament or a precursor to an antigen or a medicament. Preferably the gene construct is a chimeric gene. Preferably the spore is of *Bacillus* or *Clostridia*.

Delete paragraph number [0019] in its entirety and replace it with the following new paragraph number [0019]:

[0019] The gene construct may be under the control of one or more of, each or independently, an inducible promoter, a promoter or a strong promoter or modified promoter. The gene construct

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may have one or more enhancer elements or upstream activator sequences and the like associated with it.

Delete the paragraph inserted between paragraphs [0028] and [0029] in their entirety.

Delete paragraph number [0029] in its entirety and replace it with the following new paragraph number [0029]:

[0029] The protein used may be any that are expressed only in the vegetative state. The protein may be a protein that is expressed in the cell barrier.

Delete paragraph numbers [0032] and [0033] in their entirety and replace them with the following new paragraph numbers [0032] and [0033]:

[0032] The antigen may be a chimera with different vegetative cell proteins. By having the genetic construct encoding the antigen with a genetic construct encoding one or more different vegetative cell proteins it may be possible to provide a temporal expression of the antigen. For example, the medicament may be expressed as a chimera with a vegetative cell protein that is expressed all the time, e.g. OppA or *rrnO*, therefore providing a constant "dose" of antigen.

[0033] Alternatively, the genetic construct encoding the antigen may be with a genetic construct encoding a vegetative cell protein that is expressed intermittently and therefore upon expression of the chimera said chimera is capable of administering the medicament in a time-controlled manner. The genetic construct encoding the medicament may also be with a genetic construct of a vegetative cell protein that is expressed initially at a high concentration but which then

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decreases over time, thus upon expression, the chimera is capable of administering an initial high dose of the antigen.

Delete the paragraph inserted between paragraphs [0033] and [0034] in their entirety.

Delete paragraph number [0035] in its entirety and replace it with the following new paragraph number [0035]:

[0035] Alternatively, the genetic construct encoding the antigen may be with a genetic construct encoding a soluble cytoplasmic vegetative cell protein, e.g. *rrnO*.

Delete paragraph number [0038] in its entirety and replace it with the following new paragraph number [0038]:

[0038] According to a second aspect, the present invention provides a spore which is genetically modified with genetic code comprising a genetic construct encoding an antigen and a signal sequence, wherein said signal sequence is adapted to target said antigen to a specific part of the vegetative cell. For example, the signal sequence may direct the medicament for secretion, for example active secretion (Type I, Type II or Type III secretion), or for post-translational processing by the vegetative cell, e.g. glycosylation.

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Delete paragraph number [0044] in its entirety and replace it with the following new paragraph number [0044]:

[0044] According to a further aspect, the present invention provides according to the invention in which said spore is genetically modified with genetic code comprising at least one genetic construct encoding a medicament and a vegetative cell protein, as a chimeric gene.

Delete paragraph number [0045] in its entirety and replace it with the following new paragraph number [0045]:

[0045] The medicament may be one or more of:

Delete paragraph number [0052] in its entirety and replace it with the following new paragraph number [0052]:

[0052] According to a third aspect, the present invention provides a composition comprising a spore according to the invention in association with a pharmaceutically acceptable excipient or carrier.

Delete paragraph numbers [0054] through [0059] in their entirety and replace them with the following new paragraph numbers [0054] through [0059]:

[0054] According to a further aspect, the present invention provides a composition according to the invention for use in a method of medical treatment.

[0055] The invention also provides use of the composition according to the invention in the manufacture of the medicament for use in the treatment of a medical condition.

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[0056] A method of medical treatment would comprise treating a medical condition e.g. a disease or administering a vaccine. Medical conditions for treatment by the invention include, for example, inflammation, pain, hormonal imbalances and/or intestinal disorders.

[0057] According to a further aspect, the present invention provides a method of medical treatment, which method comprises the steps of

[0058] a) Orally administering a spore according to the invention to a person or animal in need of medical treatment;

[0059] b) Said spore germinating into a vegetative cell in the intestinal tract;